

### REMARKS

Claims 1-4 and 7-10 are pending in this application. Claims 1-3 and 7-9 stand withdrawn as being directed to a non-elected invention.

Claim 4 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* on the grounds that it would have been obvious to combine the endothelin blockers taught by Kirchengast *et al* with the selective  $\alpha_v\beta_3$  integrin antagonist taught by Srivatsa *et al*. The Office Action states that co-administration of an endothelin blocker and  $\alpha_v\beta_3$  integrin antagonist "is expected to provide efficacy at lower doses than the doses used individually, with a reduction in side effects". Applicants respectfully traverse this rejection.

First, Applicants point out that the USPTO has promulgated "Obviousness Guidelines" which should govern an obviousness analysis. The Obviousness Guidelines make clear that the *Graham* framework should be applied.

The *Graham* factors include:

- 1) determining the scope and content of the prior art;
- 2) ascertaining the differences between the claimed invention and the prior art;
- 3) resolving the level of ordinary skill in the pertinent art; and
- 4) "secondary considerations" (commercial success, long-felt but unsolved needs, failure of others, and unexpected results). 383 U.S. 1 (1966).

In *KSR*, the Supreme Court reaffirmed the *Graham* framework and stated that when the prior art is a combination of references, there still has to be some reason to combine the references:

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine

the known elements in the fashion claimed by the patent at issue. (emphasis added). *KSR v. Teleflex*, 127 S.Ct. 1727, 740-41 (2007).

Applicants respectfully submit that the Office Action fails to provide an apparent reason for combining *Srivatsa et al* and *Kirchengast et al*.

*Kirchengast et al* teach endothelin blockers and their potential utility in preventing restenosis. *Srivatsa et al* teach that selective  $\alpha_v\beta_3$  blockade is an effective anti-restenosis strategy. However, neither *Kirchengast et al* nor *Srivatsa et al* teach a pharmaceutical composition for the treatment or prevention of cardiovascular diseases comprising both an ETA endothelin blocker and an  $\alpha_v\beta_3$  integrin receptor antagonist. The Office Action's position is that such a pharmaceutical composition is *per se* obvious simply because both elements of the pharmaceutical composition were known to be separately useful for such treatment. The Office Action relies on *In re Kerkhoven*, where the CCPA stated that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose...[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980).

However, the Office Action appears to misread *In re Kerkhoven* to hold that not only is such a combination *prima facie* obvious, but it is obvious despite the presence of synergy. It is improper to simply dismiss the synergistic effect of the combination. It is well established that synergy is relevant to demonstrating unexpected results. The application demonstrates that the pig coronary restenosis models "show that the combination of ET receptor antagonists and  $\alpha_v\beta_3$  integrin receptor antagonists represents a more effective means of preventing restenosis than treatment with either drug alone." (emphasis added). See, line 44, page 17 through line 2, page 18. Further, the application also demonstrates that side effects from combination therapy are less than those from

separate treatment with each component. Accordingly, even if under *In re Kerkhoven*, the *prima facie* case of obviousness was made, Applicants have rebutted this *prima facie* case with results that demonstrate synergistic and surprising effects of the combination.

The Office Action dismisses this line of reasoning by stating that despite these synergistic and surprising effects, the components of the invention "do not co-act with each other in any new or unexpected way and define nothing patentable over the prior art." See, Office Action, at 4. However, respectfully, this is nothing but a conclusory statement devoid of any *Graham* analysis. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR v. Teleflex*, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval). See MPEP §2142 (2007).

The Office Action relies on *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273 (1976), for the proposition that when an invention consists of a combination of old elements, and the elements co-act with one another without new or different function or effect, then the claimed subject matter is obvious "without the necessity of further analysis." See, Office Action, at 4. Applicants disagree and submit that after *KSR*, the *Graham* analysis is always required to properly determine whether an invention is obvious. Moreover,

[o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR*.

The present invention is precisely the type of invention envisioned by the Court in *KSR* where further analysis is necessary. *Sakraida* is readily distinguishable because the fact patterns of *Sakraida* and the present invention are very different: *Sakraida* involved a water flush system to remove cow manure from the floor of a dairy barn. The only allegedly inventive feature was "the provision for abrupt release of the water from the tanks or pools directly onto the barn floor, which causes the flow of a sheet of water that washes all animal waste into drains within minutes and requires no supplemental hand labor." *Sakraida*, at 277. The Supreme Court recognized that both water flush systems for barns and the means for releasing the water quickly were well-known and held that it was obvious to simply re-arrange old elements to arrive at the expected result.

There is nothing remotely similar in the situation at hand to *Sakraida's* fact pattern. First, the arts are completely different. While the art in *Sakraida* is a relatively simple mechanical art, the art of the present invention is inherently unpredictable and challenging pharmaceutical research. Second, in contrast to *Sakraida*, there are very many molecules that could potentially be used to treat cardiovascular diseases. Arriving at the present invention was not simply combining a relatively small number of old elements that work similarly. Instead, it was selecting a particular combination for the treatment of cardiovascular diseases out of thousands of theoretically possible combinations.

Thus, the *Graham* inquiry does not stop simply because both elements of the claimed combination were previously used to treat cardiovascular diseases. As Applicants argued, there are a large number of elements potentially useful to treat cardiovascular diseases. It was not obvious which particular combination should be selected; and moreover, it was not obvious that the selected combination would have synergistic and other beneficial effects.

Indeed, a very large number of approaches to the treatment or prevention of restenosis and other cardiovascular diseases was known. Necessarily, the number of possible combinatorial approaches is even higher. Applicants respectfully submit that the Office Action's position would render all combinatorial approaches to disease treatment *per se* unpatentable, even when a combinatorial approach leads to synergistic results. This is not the proper result from either a legal or public policy perspective. The Office Action fails to distinguish between the fact pattern in *Sakraida*, which involves a relatively trivial combination of known elements in a relatively simple and predictable art, and the situation at hand, which involves a synergistic combination in an unpredictable art.

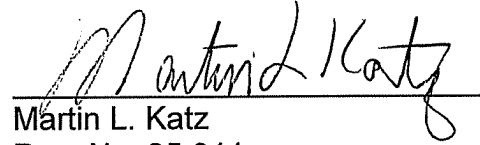
The final *Graham* factor dealing with secondary considerations also heavily weighs in favor of non-obviousness. First, there has been a long-felt but unsolved need to devise more effective treatments of cardiovascular diseases. For at least five years a) it was known that an endothelin blocker could be used to treat restenosis, b) it was known that an  $\alpha_v\beta_3$  integrin antagonist could be used to treat restenosis, and yet c) no one disclosed or suggested a combination of an endothelin blocker and  $\alpha_v\beta_3$  integrin antagonist to treat restenosis. If it were really obvious that one could easily combine these two components, then one would expect that during the five year period someone would have suggested or disclosed such a combination. The fact that nobody did so strongly suggests that the combination was not obvious to the one skilled in the art. Second, the synergy between the two components of the composition is by itself evidence of unexpected results.

Claim 10 has also been rejected under 35 U.S.C. §103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* and U.S. Patent 4,761,406. This rejection is respectfully traversed for the reasons set forth above.

Reconsideration and allowance of claims 4 and 10 is respectfully  
requested.

Respectfully submitted,

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A handwritten signature in cursive script, reading "Martin L. Katz", written over a horizontal line.

Martin L. Katz  
Reg. No. 25,011  
Wood, Phillips, Katz, Clark & Mortimer  
500 West Madison Street  
Suite 3800  
Chicago, Illinois 60661-4592  
T: 312.876.1800